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Evaluation of Induced Variance of Physical Parameters on the Calibrated USP Dissolution Apparatus 1 and 2

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The dissolution test consists of two parts; the preparation of the sample which is performed with the dissolution apparatus, and the analytical finish which is typically performed with HPLC or UV spectrophotometry. Modern dissolution apparatus provide an environment for sample preparation whereby samples removed at various times are analyzed to illustrate the rate at which the active pharmaceutical ingredient typically releases from solid oral dosage forms. Dissolution apparatus are manufactured to precisely control physical parameters, test conditions and alignment to ensure that the release of drug from a dosage form will be determined consistently from one location to another. While the dissolution test is subject to variability resulting from many sources including everything from non-rugged methodology to analyst technique, the dissolution apparatus should be well maintained and properly adjusted to consistently produce accurate and precise results. The dissolution apparatus requires calibration at predetermined intervals that "should be carried out twice a year with a performance standard." (1) The officially recognized performance standards are the USP dissolution calibrators: Prednisone 10-mg tablets and Salicylic Acid 300-mg tablets. This discussion will focus on the dissolution apparatus and the variance of specific physical parameters to demonstrate their effect on the rate of release of a sensitive pharmaceutical dosage form, the USP 10-mg Prednisone dissolution calibrator tablet.

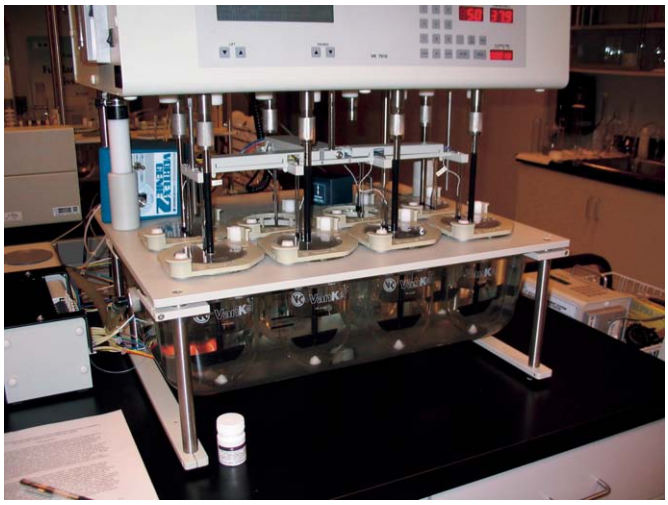

Figure 1. Vibration Induced vessel plate

Method

Temperature and vibration studies were conducted for USP Apparatus 2 (Paddle) to evaluate their potential to influence the dissolution calibrator results. Temperature was simply varied by changing the bath temperature and allowing it to stabilize at the extremes of the USP limits of 37.0 °C ± 0.5 °C. Vibration was induced by placing a Vortex Genie 2, model # G-560, on the vessel plate in the left rear corner. The Vortex Genie was placed on its side to impart vertical vibration and it was secured with tie-wraps to the left rear leg to keep it in the same location throughout testing as shown in Figure 1.

A vibration study was performed on USP Apparatus 1 (Basket) as well. Additionally, studies were conducted to evaluate modifications to the USP clip-type basket, including o-ring baskets and the 36-mesh basket conforming to the Japanese Pharmacopoeia (JP). Benchmark testing studies were performed for each apparatus with the calibrator tablets. In each case the apparatus was tuned as closely as possible to the midpoint of range parameters such as temperature (37.0 °C), rpm (50.0), height (25.0 mm) and volume (500 mL) and to minimum specifications such as wobble, vibration, centering and level as stated in the USP. This was done to obtain background data under optimum conditions for comparison to data sets containing a perturbed physical parameter or modification to the specifications outlined in USP.

The 10-mg USP Prednisone dissolution calibrator tablets (Lot # O0C056) disintegrating type were used in sets of six tablets for all analyses. All testing was conducted on a single Varian VK7010 dissolution apparatus, to allow induced vibration on the vessel plate, and samples were withdrawn with a Varian VK8000 automated dissolution sample collector. Automated equipment was utilized to eliminate the influence of manual sampling variability. Apparatus physical parameters have been adjusted as closely as possible to the exact specifications as outlined in the USP to control variability. The testing was conducted on a calibrated dissolution apparatus while main-

taining all vessels, shafts and/or baskets in their dedicated positions. Media was heated to 41 °C and vacuum degassed per USP (2). The media was measured by weight to minimize effects of volumetric variation at elevated temperature. Each test was conducted using the same methodology, media source, equipment, and analytical technique with the exception of the following parameter modifications:

- Apparatus 2 Paddles, Benchmark Study
- Apparatus 2 Paddles, Temperature 36.5 °C
- Apparatus 2 Paddles, Temperature 37.5 °C
- Apparatus 2 Paddles, Vibration @ <0.20 mils Displacement, 20 Hz
- Apparatus 2 Paddles, Vibration @ <0.02 mils Displacement, 130 Hz
- Apparatus 1 Baskets, USP clip-type 40-mesh, Benchmark Study
- Apparatus 1 Baskets, O-ring Modification 40-mesh
- Apparatus 1 Baskets, JP clip-type 36-mesh
- Apparatus 1 Baskets, USP clip-type 40 mesh, Vibration <0.20 mil displacement, 20 Hz

Paddle Test Results

The test results, in the table below, illustrate quite surprisingly that under optimum conditions there appeared to be no influence on the paddle dissolution results from fluctuations in temperature over a 1 °C range and from vibration at a level of just under 0.20 mils displacement with low frequency. In fact, the mean of six tablets was identical and close to the middle of the range, which was revised to 26%–47% for USP Apparatus 2 at 50 rpm effective December 6, 2004 (3). However, when the measured vibration frequency was increased to 130 Hz, a ten-fold drop in displacement was observed, the percent dissolved increased dramatically and produced two failing results.

Temperature

Prednisone was tested at the extremes of temperature tolerance as stated in the USP, 37.0 °C ± 0.5 °C. The Prednisone calibrator did not appear to be sensitive throughout the range of temperature specified in the USP.

Vibration

Prednisone was tested on the apparatus with the source of vibration on the vessel plate measuring below the PhRMA proposal of 0.2 mil displacement and found to be within the limits when the frequency was kept low, around 20 Hz. A ripple pattern was observed on the surface of the media but it was very slight.

A second vibration study was conducted where the vibration on the vessel plate measured <0.02 mil displacement but the frequency was increased, around 130 Hz. Even

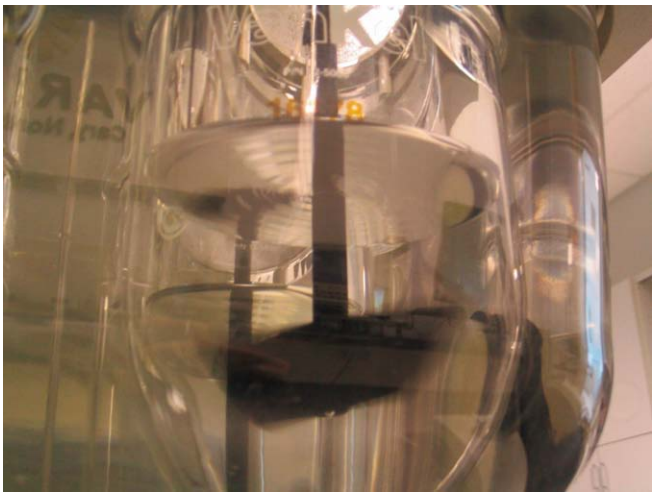

Figure 2. Vibration ripple pattern at 20 Hz.

Figure 3. Vibration ripple pattern at 130 Hz.

Table 1. Apparatus 2 at 50 rpm, USP Prednisone Lot# O0C056, range 26%–47%

	Vessel # (%)						
Perturbation	**1**	**2**	**3**	**4**	**5**	**6**	**Avg.**
Benchmark	41	34	30	33	36	32	34
Temperature 36.5 °C	37	33	30	36	34	32	34
Temperature 37.5 °C	33	37	38	30	34	29	34
Vibration @ <0.20 mils Displacement, 20 Hz	34	35	38	33	35	31	34
Vibration @ <0.02 mils Displacement, 130 Hz	53*	42	35	39	53*	31	42
(*) indicates failing data							

though there was a dramatic drop in the displacement, the destructive potential from the high frequency was evident according to the test results shown in the table above and the surface ripple pattern was sharp and distinct.

Two of six values failed to meet the USP limits. An interesting point is the location of the failing data. Referring to Figure 1, the source of vibration was placed on the left rear of the dissolution apparatus vessel plate. This probably explains why the failing data was generated from the two vessels on the left side of the dissolution apparatus; positions 1 and 5.

Basket Test Results

The next set of test results, in the table below, illustrates the influence from modifications made to the dissolution basket attachment and mesh specifications. Additionally, vibration imparted on the vessel plate at just under 0.20 mils displacement at low frequency showed marked increases in the dissolution rate that were not detected with identical conditions in the paddle test.

Table 2. Apparatus 1 Baskets at 50 rpm, USP Prednisone Lot# O0C056, range 51%–81%

	Vessel # (%)						
Perturbation	**1**	**2**	**3**	**4**	**5**	**6**	**Avg.**
USP clip-type 40-mesh, Benchmark Study	66	78	78	70	68	75	73
O-ring Modification 40-mesh	61	69	55	69	56	58	61
JP clip-type 36-mesh	73	77	71	58	71	71	70
USP clip-type 40-mesh, Vibration <0.20 mil displacement, 20 Hz	82*	75	81	77	83*	78	79
(*) indicates failing data							

Figure 4. USP clip-type (left), Unofficial O-ring attachment (right).

Attachment of Baskets

In an earlier study comparing dissolution results using O-ring and clipped basket shafts, it was noted that the USP Prednisone calibrator tablets did show a significantly different dissolution rate for the former 50-mg tablet formulation available at that time, Prednisone Lot L (4). This experiment was repeated with the 10-mg Prednisone dissolution calibrator and found to exhibit a 12% difference between the two devices. The only difference in testing was the use of the shafts as shown below.

Basket Mesh

The International Conference on Harmonization (ICH) is facilitating the standardization of the world's primary pharmacopeia to provide globally recognized testing standards. While many tests may be harmonized, questions have been raised about the ability of the dissolution baskets conforming to the various pharmacopeias to provide consistent dissolution test results. The USP and EP use a 40-mesh basket while the Japanese Pharmacopoeia describes a

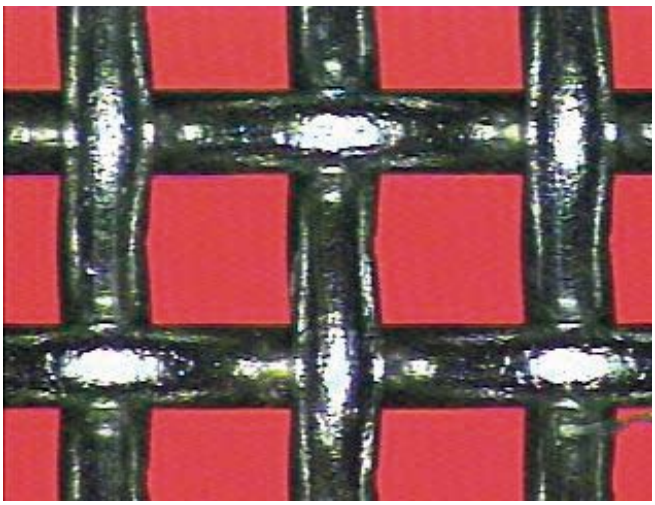

Figure 5. USP 40-mesh basket.

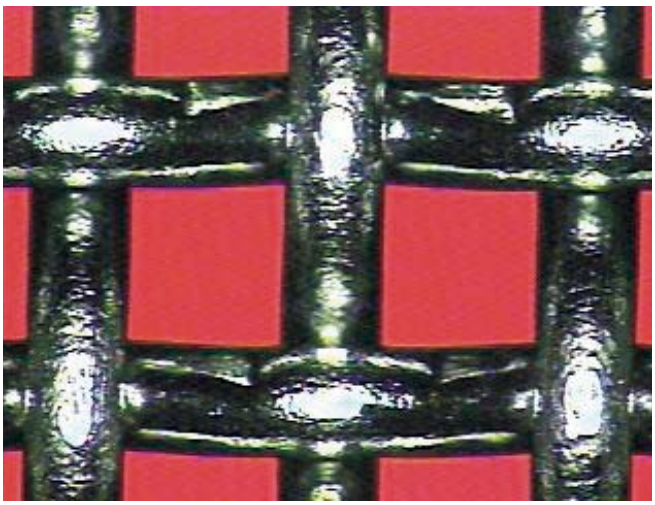

Figure 6. JP 36-mesh basket.

36-mesh specification. The test results generated for the Japanese baskets were slightly lower than the values generated with the 40-mesh basket. A side by side microscopic comparison under the same magnification demonstrates that the larger wire coupled with fewer openings in the 36-mesh basket may cause particles to be retained in the basket longer which may lead to lower dissolution results.

Summary

Although the test populations for these simple studies were relatively small, they have indicated whether induced variance has an affect on a seemingly sensitive pharmaceutical product, the USP 10-mg Prednisone dissolution calibrator tablet.

While subtle variations in temperature did not seem to influence the behavior of the Prednisone dissolution rate, the influence of vibration could be minimal or dramatic, given the consideration of frequency. The various effects of vibration found in this study correlate with a previous finding summarized in a PhRMA dissolution calibrator study on enhanced mechanical calibration; that there is a need to generate additional data to study and understand the effects of vibration on dissolution results (5). However, the results of vibration testing herein clearly indicate that displacement may not be an appropriate term to quantitate the effects of vibration. The importance of validating individual dissolution methods to study the effects of modifications to established testing standards, as outlined in the USP, becomes startlingly evident when we see a 12% decrease in test results after changing a basket attachment device from clips to an unofficial O-ring design. In the interest of good science, data generated from unofficial O-ring baskets should not be used in USP Collaborative Studies for determining the limits for the USP Calibrator tablets. Incorporation of such data will skew data downward, lowering the upper control limit which may cause unnecessary failures in the field for calibrations performed with official clip-type basket attachment. Finally, as the mesh study indicates, the need for universal and consistent testing standards, although demanded by our global economy, should not obscure our obligation to produce consistent and comparable dissolution test results.

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